CLINICAL TRIALS

Can atrial fibrillation with a coarse electrocardiographic appearance be treated with catheter ablation of the tricuspid valve–inferior vena cava isthmus? Results of a multicentre randomised controlled trial

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Heart 2007;**93**:688–693. doi: 10.1136/hrt.2006.102061

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Accepted 12 September 2006
Published Online First 28 November 2006

Objective: To see if strategy of ablating the tricuspid annulus–inferior vena cava isthmus (TV–IVC) is superior to electrical cardioversion to prevent recurrences in patients with coarse atrial fibrillation.
Design: Prospective randomised controlled multicentre study.
Setting: Four tertiary referral hospitals in the UK.
Patients: 57 patients with persistent coarse atrial fibrillation (irregular P waves ⩾0.15 mV in ⩾1 ECG lead).
Interventions: Patients were randomised to receive external cardioversion (group A, n = 30) or TV–IVC ablation +/− DC cardioversion (group B, n = 27).
Main outcome measures: Cardiac rhythm, scores on quality of life and symptom questionnaires were assessed at 4, 16 and 52 weeks after the procedure.
Results: 20 (67%) patients in group A and 19 (70%) patients in group B were in sinus rhythm immediately after their index procedure. At 4, 16 and 52 weeks, the number of patients in sinus rhythm were 5, 3 and 2 in group A and 3, 3 and 1 in group B (p = NS). The quality of life and symptom questionnaire scores were similar in the two groups at each period of follow-up, although they were significantly better for sinus rhythm than for atrial fibrillation at each follow-up visit.
Conclusions: As a first-line strategy, TV–IVC ablation offers no advantages over direct current cardioversion for the management of coarse atrial fibrillation.

Atrial fibrillation is the most common sustained cardiac arrhythmia and is a considerable burden on health-service resources.[1] The ideal treatment strategy for atrial fibrillation has been a subject of debate between proponents of the strategy of rate control and those who favour rhythm control by drugs. This uncertainty was fuelled by the equivalent results of the two strategies in large multicentre randomised trials.[2 3] However, subsequent analyses have shown that restoration of sinus rhythm is associated with symptomatic and mortality benefit, and hence this remains the ideal goal in most patients.[4–6]

However, maintenance of sinus rhythm is difficult to achieve. Although direct current cardioversion (DCCV) has a high initial success rate, less than half the patients remain in sinus rhythm at 1 year,[7] even with the use of antiarrhythmic agents.[8] An alternative approach is to remove the underlying substrate for atrial fibrillation by catheter ablation. This approach was initially developed for paroxysmal atrial fibrillation; although the techniques are evolving rapidly, the results of catheter ablation in persistent atrial fibrillation are only modest at the present time.[9]

The coexistence of atrial fibrillation and atrial flutter in the same patient is well recognised,[10 11] and the electrophysiological relationship between the two has been studied by several authors.[12 13] Using non-contact atrial mapping, we have previously shown the presence of a single consistent macro re-entry circuit in the right atrium in a proportion of patients with atrial fibrillation, whose ECG gave the appearance of coarse fibrillation waves.[14] We have shown that this circuit was defined by the same regions of conduction block as for typical right atrial flutter, in contrast with patients with fine atrial fibrillation in whom the right atrium was reactivated by breakthrough from the left atrium through the septum. We thus postulated that the underlying mechanism for coarse atrial fibrillation may be a macro re-entry circuit in the right atrium driving the atrial fibrillation by activation of the left atrium through the septum. This led us to hypothesise that a proportion of patients with atrial fibrillation with coarse P-wave morphology may be treated and recurrence of the condition prevented by isthmus catheter ablation using conventional techniques used to ablate atrial flutter.

MATERIALS AND METHODS

Study design

We performed a multicentre randomised controlled trial of tricuspid annulus–inferior vena cava isthmus (TV—IVC) ablation versus conventional treatment (DC cardioversion) in patients with persistent coarse atrial fibrillation. Four centres in the UK recruited patients for the study, and all data were stored and analysed at St Bartholomew's Hospital.

Subjects

Patients were eligible for recruitment to the trial if they had persistent atrial fibrillation (defined as lasting >7 days) with a coarse fibrillation waveform on their 12 lead ECG (irregular P waves of amplitude >0.15 mV in ⩾1 lead). All previous and present ECGs available at time of presentation were analysed for P-wave morphology, and patients were excluded if any of

Abbreviations: DCCV, direct current cardioversion; INR, International Normalised Ratio; QOL, quality of life; TV–IVC, tricuspid valve–inferior vena cava isthmus

the available 12 lead ECGs failed to meet the P-wave criterion. Patients were also excluded if they had any contraindication to catheter ablation, DC cardioversion, or systemic anticoagulation, or if they were pregnant, had a reversible cause of atrial fibrillation, were aged <18 years, had unstable ischaemic heart disease, recent (<1 month) cardiac surgery, had limited expected survival (<1 year) or needed to be on antiarrhythmic agents for arrhythmias other than atrial fibrillation/atrial flutter. The 12 lead ECG of all eligible patients were sent to the coordinating centre, where patients were randomised to group A (DC cardioversion) or group B (radiofrequency catheter ablation ± DCCV).

Procedure

All arrhythmia drugs were stopped for at least 2 weeks before the procedure. Amiodarone was also discontinued, although it is recognised that its pharmacokinetics imply continued activity during the study. All patients were anticoagulated with warfarin (aiming for an INR ⩾2) for at least 3 weeks before the study treatment.[15]

In group A, patients underwent DC cardioversion according to local guidelines. Success (defined as sinus rhythm on a 12 lead ECG immediately after the procedure) or failure was recorded. At least one 360 J shock was given before accepting failure.

In group B, patients stopped the warfarin treatment 5 days before the procedure. According to individual hospital practice, patients were then either given 3 days' supply of subcutaneous low-molecular-weight heparin to allow self-medication in the intervening period, or they underwent a transoesophageal echocardiogram immediately before the procedure to rule out the presence of thrombus.[16]

All patients in this group had a line of bidirectional isthmus conduction block created using radiofrequency energy. This could either be performed in atrial fibrillation on the basis of anatomy and electrograms, or after electrical cardioversion to sinus rhythm. If the ablation was performed before cardioversion and the patient did not return to sinus rhythm, internal cardioversion was performed, and radio frequency applied until bidirectional isthmus conduction block was proven. The method used for producing and proving isthmus conduction block was at the doctor's discretion but was a validated and recognised technique (eg, duodecapolar catheter activation and/or widely split double potentials in the isthmus during pacing).[17] Records were made of the procedure and fluoroscopy times and of the outcome, which was classified as failure, unidirectional or bidirectional isthmus conduction block.

Follow-up

All patients had ECGs performed immediately after the procedure, at discharge and at follow-up visits 4, 16 and 52 weeks after treatment. Patients were seen and ECGs recorded at other times if there was a suspicion of atrial fibrillation recurrence. Patients completed quality of life (SF-36) and symptom (modified Karolinska) questionnaires at baseline and at 4, 16 and 52 weeks follow-up visits. Patients were asked to continue warfarin for at least 1 month after cardioversion. If atrial fibrillation returned, anticoagulation was continued, and treatment with anti-arrhythmia drugs could be initiated at the discretion of the localdoctor. The subsequent management of the atrial fibrillation recurrence, including repeat electrical cardioversion if deemed suitable, was also left at the discretion of the local doctor.

End points

The primary endpoint was the incidence of sinus rhythm at 1 year without any relapse of atrial fibrillation. The secondary end points were time to onset of atrial fibrillation as determined by the 12 lead ECG, requirement for anti-arrhythmia drugs, and change in symptoms at follow-up as determined from the questionnaires.

Statistical analysis

The predicted rate of recurrence of atrial fibrillation at 1 year was 75–100% in the DC cardioversion group[7 8 18] and 29–40% in the ablation group.[11 19] Therefore, the sample size, setting the level of statistical significance at 0.05 (two-tailed) and the power at 95%, was between 18 and 110 patients to show a significant difference between the two treatment arms. We had thus aimed to recruit 120 patients into this study. However, interim analysis showed that there was no difference between the results in the two study groups and that both group of patients had an equal (high) rate of atrial fibrillation recurrence. The study coordinators decided at this point that it was inappropriate to offer TV–IVC ablation to more patients, and hence recruitment to the study was stopped in August 2005. In total, 57 patients had been enrolled in the study by this time, and the acute and follow-up results in these patients have been analysed for the purpose of this paper.

All data were analysed using an intention to treat analysis. A Kolmogorov–Smirnov test was performed on continuous variables to examine whether there was a normal distribution. This was true for patient age and for scores on the quality of life and symptom questionnaires, and these are expressed as mean (SD). All other continuous variables are expressed as median (range). Independent *t* test was used to compare between groups where data were normally distributed and a Mann–Whitney U test to compare between each group if not. For categorical data, proportions were analysed using the χ^2 test. Kaplan–Meier analysis was used to estimate freedom from atrial fibrillation and differences between the two groups measured using the Cox–Mantel-log rank test. Statistical analyses were performed using commercially available software (WinSTAT, R. Fitch Software, Bad Krozingen, Germany). A p value (two tailed) of <5% was considered significant.

RESULTS

Of the total of 113 patients considered for this trial, 57 were randomised. Of these, 14 patients had paroxysmal atrial fibrillation, 2 patients had contraindications to the radio frequency procedure, 28 patients did not meet the P-wave amplitude criterion, and 12 patients refused consent. Table 1 shows the baseline characteristics of these 57 patients. Both groups were similar with no statistically significant differences in any of the baseline characteristics, except age, which was lower in group B (55 ± 9 years versus 60 ± 10 years, p = 0.04). No patient in either group had coexistent documented atrial flutter.

Acute results

In group A, of the 30 patients randomised to electrical cardioversion, 27 actually underwent the procedure. One patient withdrew from the study after enrolment, one patient had cardioverted spontaneously and another did so when given intravenous sedation before the planned cardioversion. Of the 27 patients who underwent the procedure, 26 had an external cardioversion (mean (SD) 1.8 (1) shocks, successful energy 162.6 (65.8) J) and one had an internal cardioversion (a single 5 J shock). Of these, 18 reverted to sinus rhythm while nine continued to be in atrial fibrillation.

One patient had a large stroke 15 weeks after her successful cardioversion. She was in sinus rhythm at 4 weeks and was continuing her warfarin. Her INR was therapeutic before the cardioversion, but was seen to be only 1 when she was admitted to hospital after the stroke and was found to be in atrial fibrillation.

Table 1 Baseline characteristics

	Group A (cardioversion) n = 30	Group B (ablation) n = 27	p Value
Mean (SD) age (years)	60.2 (10)	54.7 (9.5)	0.04
Sex (male/female)	25/5	23/4	0.95
Duration of AF (months)	7 (1–72)	6 (1–180)	0.65
Previous cardioversion	13	12	0.92
Mean (SD) symptom (modified Karolinska) score	33.2 (29)	36 (21.4)	0.85
Lone AF, n	14	11	0.89
Ischaemic heart disease, n	5	4	0.93
Hypertension, n	11	11	0.87
History of alcohol excess,* n	5	7	0.68
Median current alcohol intake (units)	4.5 (0–100)	6.5 (0–30)	0.20
LV function (normal/moderate/poor)†, n	19/9/2	23/2/1	0.37
LA diameter (mm)	45 (7)	45 (6)	0.81
Mean (SD) serum potassium (mmol/l)	4.59 (0.41)	4.43 (0.38)	0.30
Mean (SD) serum creatinine (mmol/l)	101.7 (16.4)	99.7 (13.3)	0.95

AF, atrial fibrillation; LA, left atrial; LV, left ventricle.
*Alcohol excess defined as intake of >15 units/week.
†LV function classified according to calculated ejection fraction: normal (>50%), moderate (35–50%), poor (<35%)

In group B, 24 of the 27 patients randomised to this group underwent the ablation procedure. Three patients (all from one centre) could not be electrically cardioverted to sinus rhythm and were not offered the ablation procedure (protocol violation). Of the remaining 24, 12 patients were in atrial fibrillation at the time of the radio frequency procedure while the other 12 had been cardioverted to sinus rhythm. The mean (SD) procedure duration was 105 (52) min and mean (SD) fluoroscopy time was 22 (16) min. The mean (SD) number of radio frequency lesions was 12 (8). In total, 22 patients were in sinus rhythm at the end of the procedure while 2 remained in atrial fibrillation. There were 23 patients with evidence of bidirectional and 1 with clockwise isthmus conduction block at the end of the procedure. Three patients reverted to atrial fibrillation soon after the ablation procedure, thus only 19 patients were in sinus rhythm at hospital discharge. Two patients had transient ischaemic attacks 1 day after ablation. Both patients had been fully anticoagulated before and after the procedure with subcutaneous low-molecular weight heparin and were in sinus rhythm at the time of discharge.

Follow-up results

Table 2 shows the primary and secondary end points at 4, 16 and 52 weeks follow-up; the flow diagram of all 57 patients in the trial is shown in fig 1. Four patients in group A and six patients in group B had a single electrical cardioversion procedure during the follow-up period, and one patient in group B had two cardioversion procedures. The primary end point of stable sinus rhythm at 52 weeks was reached in only two patients in group A and 1 patient in group B, p = NS. The Kaplan–Meier curve for freedom from atrial fibrillation recurrence (fig 2) shows the early atrial fibrillation recurrence rate in both groups, p = 0.89, NS. The QOL and symptom questionnaire scores at 52 weeks were also similar in the two groups. As shown in table 2, the QOL scores of our population at baseline were below those of the general population, and tended to have a strong association with the cardiac rhythm throughout the follow-up period. This association was also seen with the symptom scores. Analysis of the ECGs at follow-up showed that the patients who had recurrence of atrial fibrillation had similar morphology ''coarse atrial fibrillation'' as earlier (table 3).

DISCUSSION

We have shown in this prospective randomised multicentre study that tricuspid valve–inferior vena cava isthmus (TV—IVC) ablation offers no advantages over electrical cardioversion for the management of coarse atrial fibrillation. We noted a very high incidence of early arrhythmia recurrence and as such cannot recommend this strategy as a first-line option in patients who do not have coexistent typical atrial flutter.

Treatment remains difficult for atrial fibrillation even though it is the most common arrhythmia. Although large randomised

Table 2 Follow-up results

	Group A (cardioversion)	Group B (ablation)	p Value
Acute procedure success (%)	20 (67)	19 (70)	0.86
SR at 4 weeks (%)	5 (18)	3 (12)	0.83
SR at 16 weeks (%)	3 (11)	3 (12)	0.91
SR at 52 weeks (%)	2 (7)	1 (4)	0.81
SF-36 score at 52 weeks (mean (SD))			
Physical functioning	69.4 (30)	72.1 (24.8)	0.42
Role: physical	67 (29.6)	67.2 (34.6)	0.79
Bodily pain	76.8 (27.8)	78.3 (29.2)	0.70
General health	58.2 (22.2)	60.4 (27)	0.66
Vitality	54.5 (19.5)	58 (19.8)	0.33
Social functioning	77.7 (30.1)	83.3 (24.4)	0.49
Role: emotional	77.3 (26.1)	75 (34)	0.95
Mental health	73 (22.1)	75 (18.5)	0.51
Modified Karolinska Score at 52 weeks	28.2 (26.3)	29 (24.4)	0.73

SR, sinus rhythm.

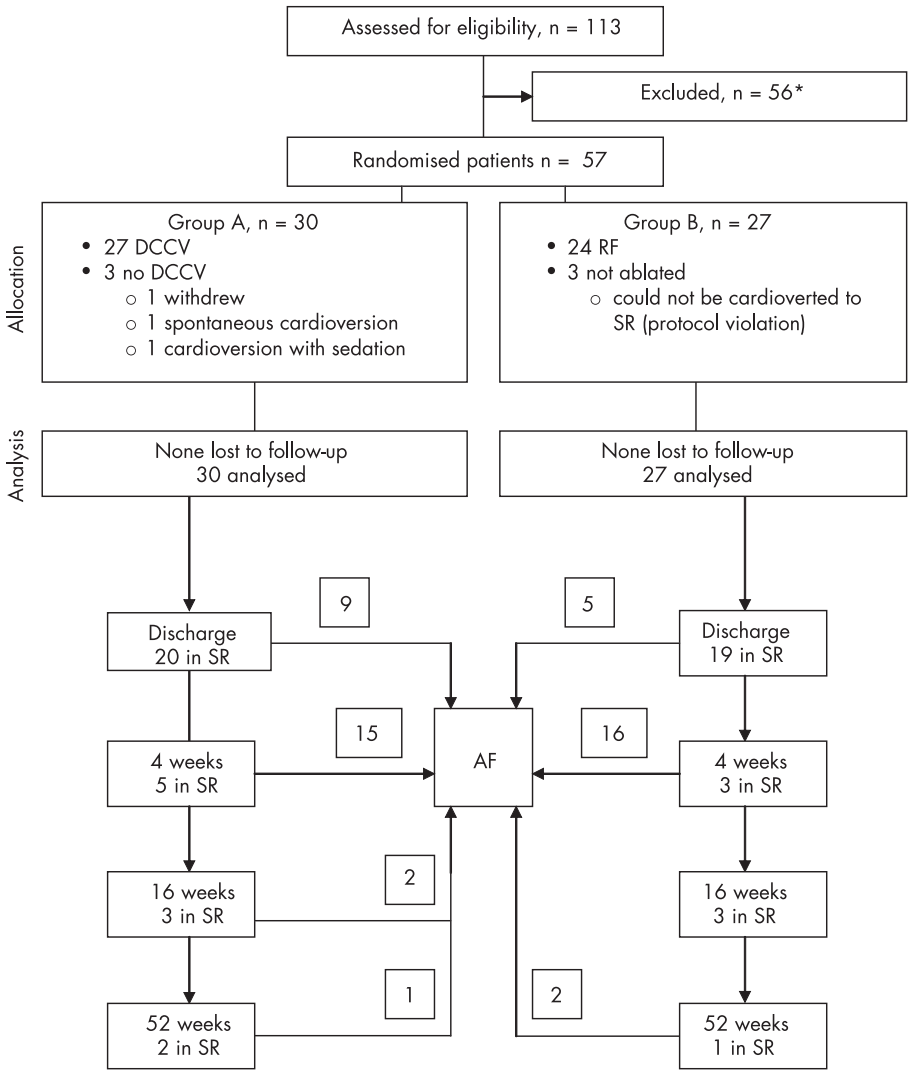

Figure 1 Flow chart of the study patients. Four patients in group A had repeat direct current cardioversion (DCCV) during follow-up. Seven patients in group B had DCCV, including one patient who had it twice; *14 patients had paroxysmal atrial fibrillation (AF), two patients had contraindications to the radio frequency (RF) procedure, 28 patients did not meet the P-wave amplitude criterion, 12 patients refused consent. SR, sinus rhythm.

trials like RACE and AFFIRM showed equivalent outcomes with the rate control and rhythm control strategies,[2 3] the results in the rhythm control group were affected by a high rate of thromboembolic complications due to premature cessation of oral anticoagulation and a high rate of adverse effects due to anti-arrhythmia drugs. Subsequent analyses have shown that morbidity and mortality were actually better in patients in whom sinus rhythm could be satisfactorily restored.[5 6 20] This has led to the view that if sinus rhythm can be maintained without adverse effects, then rhythm control should be the ideal goal.

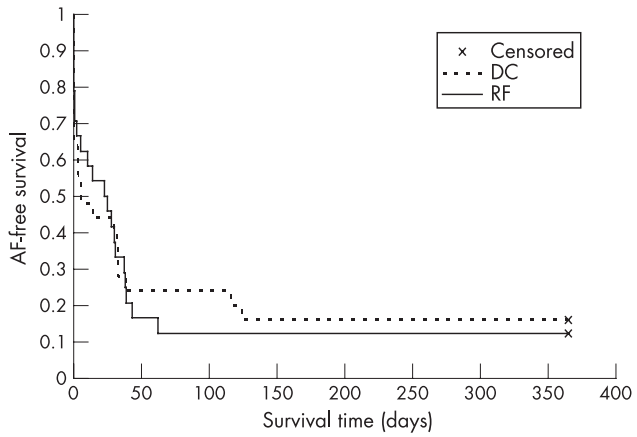

Figure 2 Kaplan–Meier survival curves for atrial fibrillation (AF)-free survival in the two groups. p=0.89 between direct current cardioversion and radio frequency (RF) groups. DC, direct current.

However, maintenance of sinus rhythm after cardioversion of atrial fibrillation is difficult to achieve. The strategy of external cardioversions with or without adjunctive treatment with anti-arrhythmia drugs is associated with only a 25–42% rate of maintenance of sinus rhythm at 1 year.[7 8] An alternative approach is to remove the underlying substrate for atrial fibrillation by catheter ablation.[21 22] This approach is becoming more popular, although it is presently more successful in treating paroxysmal than persistent atrial fibrillation. Furthermore, catheter ablation for atrial fibrillation is a complex, time-consuming procedure and is associated with a significant complication rate of up to 4–5% in routine clinical practice.[9 23] Thus, although treatment with drug for persistent atrial fibrillation has suboptimal efficacy and often unacceptable long-term side effects, the catheter ablation procedure is still a major undertaking.[24]

There is some evidence to suggest a close association between atrial fibrillation and atrial flutter. They often coexist, and

Table 3 Quality of life (SF-36) and symptom (modified Karolinska) questionnaire results at baseline and at follow-up according to cardiac rhythm

QOL domain	All patients baseline	4 weeks			16 weeks			52 weeks		
		SR	AF	p Value	SR	AF	p Value	SR	AF	p Value
Physical functioning	61.7 (28.5)	80 (22.7)	65.3(28.4)	0.03	78.1 (31.5)	63.2 (28.1)	<0.001	80.8 (31.4)	67.3 (24.2)	0.07
Role: physical	61.7 (34.5)	90.2 (10.1)	63.1 (32.3)	0.002	79.3 (29.3)	60.5 (30.2)	<0.001	73.4 (34.2)	65.4 (24.2)	0.41
Bodily pain	77.7 (28.0)	90.6 (16.4)	78.1 (26.7)	0.07	79.2 (29.3)	73.5 (28.9)	0.22	76.6 (29.5)	77.3 (28.4)	0.78
General health	62.2 (18.9)	63.6 (19.9)	55.7 (24.4)	0.06	68.5 (20.2)	51.6 (26.8)	0.05	67.3 (22.6)	55.0 (25.3)	0.23
Vitality	48.8 (23.9)	61.6 (24.0)	49.9 (26.9)	0.008	64.8 (25.9)	45.8 (22.9)	0.008	63 (17.8)	53.6 (20.2)	0.50
Social functioning	77.5 (25.9)	98.2 (4.7)	74.7 (30.0)	0.004	82.8 (27.7)	70.2 (30.2)	<0.001	90.6 (22)	76.4 (28.8)	ID
Role: emotional	66.0 (31.4)	91.6 (11.8)	72.9 (28.1)	<0.001	83.3 (25.1)	66.9 (33.2)	<0.001	88.2 (22.6)	72.1 (31.7)	ID
Mental health	70.8 (18.6)	85 (12.9)	71.4 (23.0)	0.001	80.6 (17)	66.1 (23.3)	0.04	80.4 (16.3)	70.4 (21)	0.005
Symptom (modified Karolinska)	34.1 (25.5)	10.1 (8.6)	32.8 (30.1)	0.004	18.5 (24.6)	35.7 (26.3)	0.02	20.5 (20.8)	32.8 (26.6)	0.17

AF, atrial fibrillation; ID, insufficient data; QOL, quality of life; SR, sinus rhythm.
Values are mean (SD).

typical atrial flutter can sometimes be documented after initiation of treatment with anti-arrhythmia drugs in patients with paroxysmal or persistent atrial fibrillation. It has also been shown that catheter ablation of the TV–IVC can be effective treatment for this drug-induced flutter.[10 11] In fact, ''hybrid therapy'' including TV–IVC ablation and continued treatment with anti-arrhythmia drugs has been shown to maintain sinus rhythm in these patients with atrial fibrillation.[25–27]

The electrophysiological relationship between the two arrhythmias has been studied by several authors.[12 13] By using non-contact atrial mapping we have shown the presence of a single consistent macro re-entry circuit in the right atrium in some patients with atrial fibrillation whose ECG gave the appearance of coarse fibrillation waves.[14] This circuit was defined by the same regions of conduction block as for typical right atrial flutter. This was in contrast to the picture seen in patients with fine atrial fibrillation, where periods of electrical silence were common and the right atrium was reactivated by breakthrough from the left atrium through the septum. We had thus postulated that the underlying mechanism for coarse atrial fibrillation may be a macro re-entry circuit in the right atrium driving the atrial fibrillation by activation of the left atrium through the septum. This led us to hypothesise that atrial fibrillation with coarse P-wave morphology may be treated and its recurrence prevented by catheter ablation using conventional techniques used to ablate atrial flutter. If successfully proven, this hypothesis had the potential to offer a simpler procedure for treating at least a subset of patients with atrial fibrillation by catheter ablation.

However, we have shown that as a first-line strategy, TV–IVC ablation offers no advantages over electrical cardioversion for the management of coarse atrial fibrillation. Atrial fibrillation recurred in most patients soon after successful isthmus ablation, and their quality of life and symptom scores then worsened. This perhaps supports the hypothesis that most cases of atrial fibrillation are driven by the left atrium.[28 29] Our study results also suggest that routine TV–IVC isthmus ablation as a component of an atrial fibrillation ablation procedure is probably unnecessary in the absence of previous clearly documented atrial flutter. Our results differ from those of others who have shown that hybrid therapy with isthmus ablation and drug treatment can prevent recurrences of atrial fibrillation. However, our patients were different in that they had no prior history of atrial flutter. We also observed that the recurrent atrial fibrillation in almost all our cases was similar in morphology to the initial fibrillation—that is, with a coarse P-wave morphology. This suggests that simple analysis of P-wave morphology may have a limited role in characterising the mechanism of underlying atrial fibrillation in individual patients.

Our data also highlight three important points regarding management of these patients with atrial fibrillation. The first is the need for aggressive anticoagulation, especially in the immediate post-cardioversion period. Our one major complication (stroke after successful DC cardioversion) was associated with subtherapeutic INR and recurrence of atrial fibrillation. Our study also confirms the futility of DC cardioversion in maintaining stable sinus rhythm at follow-up, as borne out by several prior studies.[7 8 18] Lastly, we saw a very strong association between sinus rhythm and improvement in quality of life and symptoms. Many patients only became aware of the deleterious effect that atrial fibrillation was having on their quality of life when they went from atrial fibrillation to sinus rhythm and then back to atrial fibrillation again. This suggests that the risks and complexity of the current ablative techniques for persistent atrial fibrillation may prove to be worthwhile.

Limitations of the study

One limitation of this study is its relative small size and the fact that we stopped recruitment when only half the intended numbers had been enrolled. However, the lack of benefit of isthmus ablation was so consistent among the study centres on interim analysis that it was considered inappropriate to continue to offer this procedure to patients. Kaplan–Meier analysis also showed a very early recurrence of atrial fibrillation in both treatment groups, and it seems highly unlikely that a larger study population would have brought out a meaningful difference. We also did not attempt to confirm or exclude the role of the TV–IVC in the coarse atrial fibrillation circuit in these patients as we had done previously.[14] This was deliberate however, as we wanted to minimise the complexity of the ablation procedure and felt that any likely future merit in this procedure would lie in its simplicity.

CONCLUSION

We have shown in this multicentre prospective randomised study that TV–IVC ablation offers no advantages over DCCV for the management of coarse atrial fibrillation.

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Funding: We are grateful to the British Heart Foundation for their support with funding.

Competing interests: None.

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